

Inventor : DONG, Zheng Xin et al.
Serial No. : 09/856,676
Filed : July 16, 2001
Page : 4

COMPLETE LISTING OF ALL CLAIMS, WITH MARKINGS AND STATUS IDENTIFIERS
(Currently amended claims showing deletions by ~~striketrough~~ and
additions by underlining)

What is claimed is:

1 (original): A compound of formula (I),
(R²R³)- A⁷-A⁸-A⁹-A¹⁰-A¹¹-A¹²-A¹³-A¹⁴-A¹⁵-A¹⁶-A¹⁷-A¹⁸-A¹⁹-A²⁰
-A²¹-A²²-A²³-A²⁴-A²⁵-A²⁶-A²⁷-A²⁸-A²⁹-A³⁰-A³¹-A³²-A³³-A³⁴-A³⁵-
A³⁶-A³⁷-R¹,

(I)

wherein

A⁷ is L-His, Ura, Paa, Pta, D-His, Tyr, 3-Pal, 4-Pal, Hppa, Tma-His, Amp or deleted, provided that when A⁷ is Ura, Paa, Pta or Hppa then R² and R³ are deleted;

A⁸ is Ala, D-Ala, Aib, Acc, N-Me-Ala, N-Me-D-Ala, Arg or N-Me-Gly;

A⁹ is Glu, N-Me-Glu, N-Me-Asp or Asp;

A¹⁰ is Gly, Acc, Ala, D-Ala, Phe or Aib;

A¹¹ is Thr or Ser;

A¹² is Phe, Acc, Aic, Aib, 3-Pal, 4-Pal, β-Nal, Cha, Trp or X¹-Phe;

A¹³ is Thr or Ser;

A¹⁴ is Ser, Thr, Ala or Aib;

A¹⁵ is Asp, Ala, D-Asp or Glu;

A¹⁶ is Val, D-Val, Acc, Aib, Leu, Ile, Tle, Nle, Abu, Ala, D-Ala, Tba or Cha;

A¹⁷ is Ser, Ala, D-Ala, Aib, Acc or Thr;

A¹⁸ is Ser, Ala, D-Ala, Aib, Acc or Thr;

A¹⁹ is Tyr, D-Tyr, Cha, Phe, 3-Pal, 4-Pal, Acc, β-Nal, Amp or X¹-Phe;

A²⁰ is Leu, Ala, Acc, Aib, Nle, Ile, Cha, Tle, Val, Phe or X¹-Phe;

A²¹ is Glu, Ala or Asp;

A²² is Gly, Acc, Ala, D-Ala, β-Ala or Aib;

A²³ is Gln, Asp, Ala, D-Ala, Aib, Acc, Asn or Glu;

A²⁴ is Ala, Aib, Val, Abu, Tle or Acc;

A²⁵ is Ala, Aib, Val, Abu, Tle, Acc, Lys, Arg, hArg, Orn,
 HN-CH((CH₂)_n-NR¹⁰R¹¹)-C(O) or HN-CH((CH₂)_e-X³)-C(O);

A²⁶ is Lys, Ala, 3-Pal, 4-Pal, Arg, hArg, Orn, Amp,
 HN-CH((CH₂)_n-NR¹⁰R¹¹)-C(O) or HN-CH((CH₂)_e-X³)-C(O);

A²⁷ is Glu, Ala, D-Ala or Asp;

A²⁸ is Phe, Ala, Pal, β-Nal, X¹-Phe, Aic, Acc, Aib, Cha or
 Trp;

A²⁹ is Ile, Acc, Aib, Leu, Nle, Cha, Tle, Val, Abu, Ala, Tba
 or Phe;

A³⁰ is Ala, Aib, Acc or deleted;

A³¹ is Trp, Ala, β-Nal, 3-Pal, 4-Pal, Phe, Acc, Aib, Cha, Amp
 or deleted;

A³² is Leu, Ala, Acc, Aib, Nle, Ile, Cha, Tle, Phe, X¹-Phe,
 Ala or deleted;

A³³ is Val, Acc, Aib, Leu, Ile, Tle, Nle, Cha, Ala, Phe, Abu,
 X¹-Phe, Tba, Gaba or deleted;

A³⁴ is Lys, Arg, hArg, Orn, Amp, Gaba,
 HN-CH((CH₂)_n-NR¹⁰R¹¹)-C(O), HN-CH((CH₂)_e-X³)-C(O) or deleted;

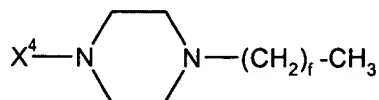
A³⁵ is Gly or deleted;

A³⁶ is L- or D-Arg, D- or L-Lys, D- or L-hArg, D- or L-Orn,
 Amp, HN-CH((CH₂)_n-NR¹⁰R¹¹)-C(O), HN-CH((CH₂)_e-X³)-C(O) or
 deleted;

A³⁷ is Gly or deleted;

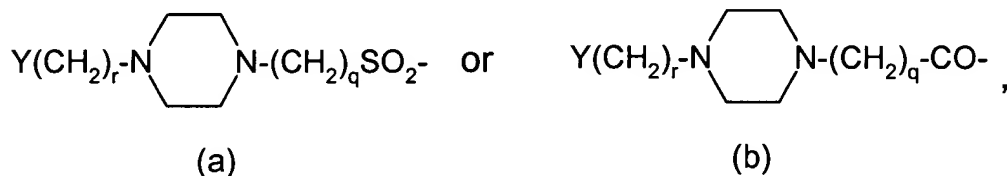
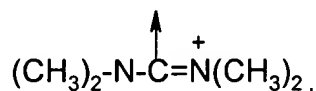
X¹ for each occurrence is independently selected from
 the group consisting of (C₁-C₆)alkyl, OH and halo;

R¹ is OH, NH₂, (C₁-C₁₂)alkoxy, or NH-X²-CH₂-Z, wherein X²
 is a (C₁-C₁₂)hydrocarbon moiety, and Z is H, OH, CO₂H or
 CONH₂;

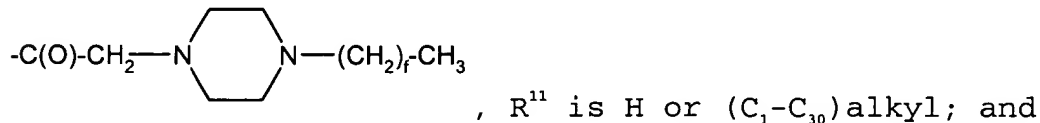
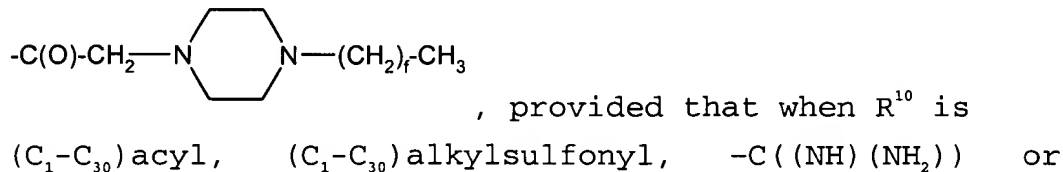


X³ is or -C(O)-NHR¹², wherein X⁴ for
 each occurrence is independently -C(O)-, -NH-C(O)- or
 -CH₂-, and f for each occurrence is independently an
 integer from 1 to 29;

each of R² and R³ is independently selected from the group consisting of H, (C₁-C₃₀)alkyl, (C₂-C₃₀)alkenyl, phenyl(C₁-C₃₀)alkyl, naphthyl(C₁-C₃₀)alkyl, hydroxy(C₁-C₃₀)alkyl, hydroxy(C₂-C₃₀)alkenyl, hydroxyphenyl(C₁-C₃₀)alkyl, and hydroxynaphthyl(C₁-C₃₀)alkyl; or one of R² and R³ is C(O)X⁵ in which X⁵ is (C₁-C₃₀)alkyl, (C₂-C₃₀)alkenyl, phenyl(C₁-C₃₀)alkyl, naphthyl(C₁-C₃₀)alkyl, hydroxy(C₁-C₃₀)alkyl, hydroxy(C₂-C₃₀)alkenyl, hydroxyphenyl(C₁-C₃₀)alkyl, hydroxynaphthyl(C₁-C₃₀)alkyl,



where Y is H or OH, r is 0 to 4 and q is 0 to 4;
 e for each occurrence is independently an integer from 1 to 4;
 n for each occurrence is independently an integer from 1-5; and
 R¹⁰ and R¹¹ for each occurrence is each independently H, (C₁-C₃₀)alkyl, (C₁-C₃₀)acyl, (C₁-C₃₀)alkylsulfonyl, -C((NH)(NH₂)) or



R¹² is (C₁-C₃₀)alkyl;

with the proviso that:

(i) at least one amino acid of a compound of formula (I) is not the same as the native sequence of hGLP-1(7-36, or

-37)NH₂ (SEQ ID NOS: 1, 2) or hGLP-1(7-36, or -37)OH (SEQ ID NOS: 3, 4);

(ii) a compound of formula (I) is not an analogue of hGLP-1(7-36, or -37)NH₂ (SEQ ID NOS: 1,2) or hGLP-1(7-36, or -37)OH (SEQ ID NOS: 3, 4) wherein a single position has been substituted by Ala;

(iii) a compound of formula (I) is not

[Lys²⁶(N^ε-alkanoyl)]hGLP-1(7-36, or -37)-E (SEQ ID NOS: 5-8),

[Lys³⁴(N^ε-alkanoyl)]hGLP-1(7-36, or -37)-E (SEQ ID NOS: 9-12),

[Lys^{26,34}-bis(N^ε-alkanoyl)]hGLP-1(7-36, or -37)-E (SEQ ID NOS:

13-16), [Arg²⁶, Lys³⁴(N^ε-alkanoyl)]hGLP-1(8-36, or -37)-E (SEQ

ID NOS: 17-20), or [Arg^{26,34}, Lys³⁶(N^ε-alkanoyl)]hGLP-1(7-36, or -37)-E, wherein E is -OH or -NH₂ (SEQ ID NOS: 21-24);

(iv) a compound of formula (I) is not

Z-hGLP-1(7-36, or -37)-OH, Z-hGLP-1(7-36, or -37)-NH₂, where Z is selected from the group consisting of

(a) [Arg²⁶] (SEQ ID NOS: 25-28), [Arg³⁴] (SEQ ID NOS: 29-32),

[Arg^{26,34}] (SEQ ID NOS: 33-36), [Lys³⁶], [Arg²⁶, Lys³⁶] (SEQ ID

NOS: 41-44), [Arg³⁴, Lys³⁶] (SEQ ID NOS: 45-46), [D-Lys³⁶],

[Arg³⁶] (SEQ ID NOS: 37-40), [D-Arg³⁶] (SEQ ID NOS: 3, 4, 1,

2), [Arg^{26,34}, Lys³⁶] (SEQ ID NOS: 49-52) or [Arg^{26,36}, Lys³⁴]

(SEQ ID NOS: 25-28);

(b) [Asp²¹] (SEQ ID NOS: 53-56);

(c) at least one of [Aib⁸] (SEQ ID NOS: 57-60), [D-Ala⁸] and

[Asp⁹] (SEQ ID NOS: 61-64); and

(d) [Tyr⁷] (SEQ ID NOS: 65-68), [N-acyl-His⁷] (SEQ ID NOS: 69-

72), [N-alkyl-His⁷] (SEQ ID NOS: 73-76), [N-acyl-D-His⁷] or

[N-alkyl-D-His⁷];

(v) a compound of formula (I) is not a combination of any two of the substitutions listed in groups (a) to (d); and

(vi) a compound of formula (I) is not [N-Me-Ala⁸]hGLP-1(8-36

or -37) (SEQ ID NOS: 77, 78), [Glu¹⁵]hGLP-1(7-36 or -37) (SEQ

ID NOS: 79, 80), [Asp²¹]hGLP-1(7-36 or -37) (SEQ ID NOS: 53,

54) or [Phe³¹]hGLP-1(7-36 or -37) (SEQ ID NOS: 81, 82).

2 (original): A compound according to claim 1 or a pharmaceutically acceptable salt thereof wherein A¹¹ is Thr; A¹³ is Thr; A¹⁴ is Ser, Aib or Ala; A¹⁷ is Ser, Ala, Aib or

D-Ala; A¹⁸ is Ser, Ala, Aib or D-Ala; A²¹ is Glu or Ala; A²³ is Gln, Glu, or Ala; and A²⁷ is Glu or Ala.

3 (original): A compound according to claim 2 or a pharmaceutically acceptable salt thereof wherein A⁹ is Glu, N-Me-Glu or N-Me-Asp; A¹² is Phe, Acc or Aic; A¹⁶ is Val, D-Val, Acc, Aib, Ala, Tle or D-Ala; A¹⁹ is Tyr, 3-Pal, 4-Pal or D-Tyr; A²⁰ is Leu, Acc, Cha, Ala or Tle; A²⁴ is Ala, Aib or Acc; A²⁵ is Ala, Aib, Acc, Lys, Arg, hArg, Orn,

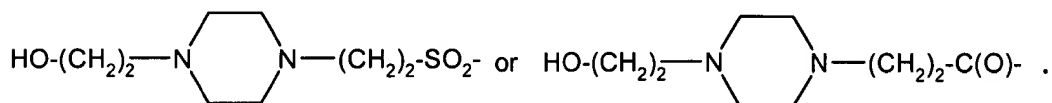
HN-CH((CH₂)_n-NH-R¹⁰)-C(O); A²⁸ is Phe or Ala; A²⁹ is Ile, Acc or Tle; A³⁰ is Ala, Aib or deleted; A³¹ is Trp, Ala,

3-Pal, 4-Pal or deleted; A³² is Leu, Acc, Cha, Ala or deleted; A³³ is Val, Acc, Ala, Gaba, Tle or deleted.

4 (original): A compound according to claim 3 or a pharmaceutically acceptable salt thereof wherein A⁸ is Ala, D-Ala, Aib, A6c, A5c, N-Me-Ala, N-Me-D-Ala or N-Me-Gly; A¹⁰ is Gly, Ala, D-Ala or Phe; A¹² is Phe, A6c or A5c; A¹⁶ is Val, Ala, Tle, A6c, A5c or D-Val; A²⁰ is Leu, A6c, A5c, Cha, Ala or Tle; A²² is Gly, Aib, β-Ala, L-Ala or D-Ala; A²⁴ is Ala or Aib; A²⁹ is Ile, A6c, A5c or Tle; A³² is Leu, A6c, A5c, Cha, Ala or deleted; A³³ is Val, A6c, A5c, Ala, Gaba, Tle or deleted.

5 (original): A compound according to claim 4 or a pharmaceutically acceptable salt thereof wherein R¹ is OH or NH₂.

6 (original): A compound according to claim 5 or a pharmaceutically acceptable salt thereof wherein R² is H and R³ is (C₁-C₃₀)alkyl, (C₂-C₃₀)alkenyl, (C₁-C₃₀)acyl,



7 (original): A compound according to claim 1
wherein said compound is

[D-Ala⁸, Ala^{17,22,23,27}, 3-Pal^{19,31}, Gaba³⁴]-GLP-1(7-34)NH₂;
[D-Ala^{8,23,27}, 3-Pal^{19,31}]hGLP-1(7-35)-NH₂;
[Ala^{18,23,27}, 3-Pal^{19,31}]hGLP-1(7-35)-NH₂ (SEQ ID NO: 83);
[Ala^{16,23,27}, 3-Pal^{19,31}]hGLP-1(7-35)-NH₂ (SEQ ID NO: 84);
[Ala^{14,23,27}, 3-Pal^{19,31}]hGLP-1(7-35)-NH₂ (SEQ ID NO: 85);
[Ala^{22,23,27}, 3-Pal^{19,31}]hGLP-1(7-35)-NH₂ (SEQ ID NO: 86);
[Hppa⁷]hGLP-1(7-36)-NH₂ (SEQ ID NO: 87);
[Ala^{15,23,27}, 3-Pal^{19,31}]hGLP-1(7-35)-NH₂ (SEQ ID NO: 88);
[Ala^{17,23,27}, 3-Pal^{19,31}]hGLP-1(7-35)-NH₂ (SEQ ID NO: 89);
[Ala^{22,23,27}, 3-Pal^{19,31}, Gaba³⁴]hGLP-1(7-34)-NH₂ (SEQ ID NO: 90);
[Ala^{15,22,23,27}, 3-Pal^{19,31}, Gaba³⁴]hGLP-1(7-34)-NH₂ (SEQ ID NO: 91);
[Ala^{17,22,23,27}, 3-Pal^{19,31}, Gaba³⁴]hGLP-1(7-34)-NH₂ (SEQ ID NO: 92);
[Ala^{18,22,23,27}, 3-Pal^{19,31}, Gaba³⁴]hGLP-1(7-34)-NH₂ (SEQ ID NO: 93);
[Ala^{21,22,23,27}, 3-Pal^{19,31}, Gaba³⁴]hGLP-1(7-34)-NH₂ (SEQ ID NO: 94);
[Ala^{22,23,26,27}, 3-Pal^{19,31}, Gaba³⁴]hGLP-1(7-34)-NH₂ (SEQ ID NO: 95);
[Ala^{22,23,27,32}, 3-Pal^{19,31}, Gaba³⁴]hGLP-1(7-34)-NH₂ (SEQ ID NO: 96);
[Ala^{22,23,26,27}, 3-Pal^{19,31}, Gaba³³]hGLP-1(7-33)-NH₂ (SEQ ID NO: 97);
[Ala^{22,23,27,31}, 3-Pal¹⁹, Gaba³³]hGLP-1(7-33)-NH₂ (SEQ ID NO: 98);
[Ala^{22,23,27,28}, 3-Pal^{19,31}, Gaba³³]hGLP-1(7-33)-NH₂ (SEQ ID NO: 99);
[Ala^{22,23,27,29}, 3-Pal^{19,31}, Gaba³³]hGLP-1(7-33)-NH₂ (SEQ ID NO: 100);
[Ala^{23,27}, 3-Pal^{19,31}, Gaba³³]hGLP-1(7-33)-NH₂ (SEQ ID NO: 101);
[Ala^{20,22,23,27}, 3-Pal^{19,31}, Gaba³³]hGLP-1(7-33)-NH₂ (SEQ ID NO:
102);
[Ala^{22,23,27}, 3-Pal^{19,31}, Gaba³³]hGLP-1(7-33)-NH₂ (SEQ ID NO: 103);
[Ala^{17,22,23,27}, 3-Pal^{19,31}, Gaba³³]hGLP-1(7-33)-NH₂ (SEQ ID NO:
104);
[D-Ala¹⁰, Ala^{22,23,27}, 3-Pal^{19,31}, Gaba³³]hGLP-1(7-33)-NH₂;
[D-Ala⁸, Ala^{17,23,27}, 3-Pal^{19,31}]hGLP-1(7-34)-NH₂;
[Ala^{17,23,27}, 3-Pal^{19,26,31}]hGLP-1(7-34)-NH₂ (SEQ ID NO: 105);
[D-Ala⁸, Ala¹⁷, 3-Pal^{19,31}]hGLP-1(7-34)-NH₂;
[Ala^{17,23,27}, 3-Pal^{19,31}]hGLP-1(7-34)-NH₂ (SEQ ID NO: 106);
[D-Ala⁸, Ala^{17,23,27}, 3-Pal^{19,31}, Tle²⁹]hGLP-1(7-34)-NH₂;

[D-Ala⁸, Ala^{17,23,27}, 3-Pal^{19,31}, Tle¹⁶]hGLP-1(7-34)-NH₂;
[D-Ala⁸, Ala^{17,23,27}, 3-Pal^{19,31}, Gaba³⁴]hGLP-1(7-34)-NH₂;
[D-Ala²², Ala^{17,23,27}, 3-Pal^{19,31}, Gaba³⁴]hGLP-1(7-34)-NH₂;
[Aib⁸, Ala^{17,23,27}, 3-Pal^{19,31}, Gaba³⁴]hGLP-1(7-34)-NH₂ (SEQ ID NO:
107);
[D-Ala⁸, Ala^{17,22,23,27}, 3-Pal^{19,31}]hGLP-1(7-33)-NH₂;
[Aib⁸, Ala^{17,22,23,27}, 3-Pal^{19,31}]hGLP-1(7-33)-NH₂ (SEQ ID NO: 108);
[Ala^{17,18,23,27}, 3-Pal^{19,31}, Gaba³⁴]hGLP-1(7-34)-NH₂ (SEQ ID NO:
109);
[Ala^{17,23,27}, 3-Pal^{19,31}, Tle³³, Gaba³⁴]hGLP-1(7-34)-NH₂ (SEQ ID NO:
110);
[Tle¹⁶, Ala^{17,23,27}, 3-Pal^{19,31}, Gaba³⁴]hGLP-1(7-34)-NH₂ (SEQ ID NO:
111);
[N-Me-D-Ala⁸, Ala^{17,22,23,27}, 3-Pal^{19,31}]hGLP-1(7-33)-NH₂;
[Aib⁸, Ala^{17,18,22,23,27}, 3-Pal^{19,31}]hGLP-1(7-33)-NH₂ (SEQ ID NO:
112);
[Ala^{17,18,22,23,27}, 3-Pal^{19,31}, Tle^{16,20}, Gaba³⁴]hGLP-1(7-34)-NH₂ (SEQ ID
NO: 113);
[D-Ala⁸, Ala^{17,18,22,23,27}, 3-Pal^{19,31}, Tle¹⁶, Gaba³⁴]hGLP-1(7-34)-NH₂;
[D-Ala^{8,22}, Ala^{17,18,23,27}, 3-Pal^{19,31}, Gaba³⁴]hGLP-1(7-34)-NH₂;
[D-Ala^{8,18}, Ala^{17,22,23,27}, 3-Pal^{19,31}, Gaba³⁴]hGLP-1(7-34)-NH₂;
[D-Ala^{8,17}, Ala^{18,22,23,27}, 3-Pal^{19,31}, Gaba³⁴]hGLP-1(7-34)-NH₂; or
[D-Ala⁸, Ala^{17,18,22,23,27}, 3-Pal^{19,31}, Gaba³⁴]hGLP-1(7-34)-NH₂; or a
pharmaceutically acceptable salt thereof.

8 (original): A compound according to claim 1
wherein said compound is

[Aib⁸, A6c³²]hGLP-1(7-36)NH₂ (SEQ ID NO: 114);
[A6c^{20,32}]hGLP-1(7-36)-NH₂ (SEQ ID NO: 115);
[Aib⁸]hGLP-1(7-36)-NH₂ (SEQ ID NO: 116);
[(Tma-His)⁷]hGLP-1(7-36)-NH₂ (SEQ ID NO: 117);
[A6c⁸]hGLP-1(8-36)-NH₂ (SEQ ID NO: 118);
[A6c⁸]hGLP-1(7-36)-NH₂ (SEQ ID NO: 119);
[A6c^{16,20}]hGLP-1(7-36)-NH₂ (SEQ ID NO: 120);
[A6c^{29,32}]hGLP-1(7-36)-NH₂ (SEQ ID NO: 121);
[A6c²⁰, Aib²⁴]hGLP-1(7-36)-NH₂ (SEQ ID NO: 122);

[Aib²⁴, A6c^{29,32}]hGLP-1(7-36)-NH₂ (SEQ ID NO: 123);
[A6c^{16,29,32}]hGLP-1(7-36)-NH₂ (SEQ ID NO: 124);
[Ura⁷]hGLP-1(7-36)-NH₂ (SEQ ID NO: 125);
[Paa⁷]hGLP-1(7-36)-NH₂ (SEQ ID NO: 126);
[Pta⁷]hGLP-1(7-36)-NH₂ (SEQ ID NO: 127);
[N-Me-Ala⁸]hGLP-1(7-36)-NH₂ (SEQ ID NO: 128);
[N-Me-D-Ala⁸]hGLP-1(7-36)-NH₂;
[N-Me-D-Ala⁸]hGLP-1(8-36)-NH₂;
[N-Me-Gly⁸]hGLP-1(7-36)-NH₂ (SEQ ID NO: 129);
[A5c⁸]hGLP-1(7-36) (SEQ ID NO: 130) ;
[N-Me-Glu⁹]hGLP-1(7-36)-NH₂ (SEQ ID NO: 131);
[A5c⁸, A6c^{20,32}]hGLP-1(7-36)-NH₂ (SEQ ID NO: 132);
[Aib⁸, A6c³²]hGLP-1(7-36)-NH₂ (SEQ ID NO: 133);
[Aib^{8,25}]hGLP-1(7-36)-NH₂ (SEQ ID NO: 134);
[Aib^{8,24}]hGLP-1(7-36)-NH₂ (SEQ ID NO: 135);
[Aib^{8,30}]hGLP-1(7-36)-NH₂ (SEQ ID NO: 136);
[Aib⁸, Cha²⁰]hGLP-1(7-36)-NH₂ (SEQ ID NO: 137);
[Aib⁸, Cha³²]hGLP-1(7-36)-NH₂ (SEQ ID NO: 138);
[Aib⁸, Glu²³]hGLP-1(7-36)-NH₂ (SEQ ID NO: 139);
[Aib⁸, A6c²⁰]hGLP-1(7-36)-NH₂ (SEQ ID NO: 140);
[Aib⁸, A6c^{20,32}]hGLP-1(7-36)-NH₂ (SEQ ID NO: 141);
[Aib^{8,22}]hGLP-1(7-36)-NH₂ (SEQ ID NO: 142);
[Aib⁸, β-Ala²²]hGLP-1(7-36)-NH₂ (SEQ ID NO: 143);
[Aib⁸, Lys²⁵]hGLP-1(7-36)-NH₂ (SEQ ID NO: 144);
[Aib⁸, A6c¹²]hGLP-1(7-36)-NH₂ (SEQ ID NO: 145);
[Aib⁸, A6c²⁹]hGLP-1(7-36)-NH₂ (SEQ ID NO: 146);
[Aib⁸, A6c³³]hGLP-1(7-36)-NH₂ (SEQ ID NO: 147);
[Aib^{8,14}]hGLP-1(7-36)NH₂ (SEQ ID NO: 148);
[Aib^{8,18}]hGLP-1(7-36)NH₂ (SEQ ID NO: 149); or
[Aib^{8,17}]hGLP-1(7-36)NH₂ (SEQ ID NO: 150); or a
pharmaceutically acceptable salt thereof.

9 (original): A pharmaceutical composition
comprising an effective amount of a compound according to

claim 1 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent.

10 (withdrawn): A method of eliciting an agonist effect from a GLP-1 receptor in a subject in need thereof which comprises administering to said subject an effective amount of a compound according to claim 1 or a pharmaceutically acceptable salt thereof.

11 (withdrawn): A method of treating a disease selected from the group consisting of Type I diabetes, Type II diabetes, obesity, glucagonomas, secretory disorders of the airway, metabolic disorder, arthritis, osteoporosis, central nervous system disease, restenosis, neurodegenerative disease, renal failure, congestive heart failure, nephrotic syndrome, cirrhosis, pulmonary edema, and hypertension, in a subject in need thereof which comprises administering to said subject an effective amount of a compound according to claim 1 or a pharmaceutically acceptable salt thereof.

12 (withdrawn): A method according to claim 11 wherein said disease is Type I diabetes or Type II diabetes.